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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,502	05/18/2001	Michel Sadelain	MSK.P-040	1539
52334	7590	05/25/2006	EXAMINER	
Marina Larson & Associates LLC re: MSK P. O. BOX 4928 DILLON, CO 80435-4928			RAWLINGS, STEPHEN L	
			ART UNIT	PAPER NUMBER
			1643	

DATE MAILED: 05/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 December 2005 and 18 February 2006.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-3,5,7,8,10-13,16,21-26,28-30 and 32 is/are pending in the application.
- 4a) Of the above claim(s) 7,8,10,11 and 21-24 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-3,5,12,13,16,25,26,28-30 and 32 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 01 March 2001 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

1. The response filed February 18, 2006, is acknowledged and has been entered.
2. The amendment filed December 15, 2005, is acknowledged and has been entered. Claims 1, 5, 12, 25, 26, and 28 have been amended.
3. Claims 1-3, 5, 7, 8, 10-13, 16, 21-26, 28-30, and 32 are pending in the application. Claims 7, 8, 10, 11, and 21-24 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 29, 2002.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
5. Claims 1-3, 5, 12, 13, 16, 25, 26, 28-30, and 32 are currently under prosecution.

Response to Arguments

6. Applicant's argument submitted in the response filed February 18, 2006, with respect to the objection of the amendment filed September 8, 2003, as set forth in section 7 of the prior Office action mailed September 21, 2005, has been carefully considered but not found persuasive for the following reasons:

As noted in the prior Office communication mailed March 9, 2006, Applicant has argued that the amendment did not introduce new matter. Applicant has asserted that the ordinary meaning of the term "spanning" is "going across", and therefore, given the original disclosure of the CD28 cytoplasmic domain, which is "particularly a fragment spanning amino acids 336 to 663 of CD28 cDNA", it would be understood that the CD28 fragment comprises the amino acids encoded by bases including bases 336 to 663 of the cDNA encoding CD28.

Again, a span is the distance between two points¹; therefore, “spanning” would ordinarily be understood to mean, “extending from one point to another”². Contrary to Applicant’s assertion, the term “spanning” would not be understood to mean “extending from one point to another, *and beyond in either direction*”.

Furthermore, as explained in Office action mailed September 21, 2005, the originally filed disclosures at pages 6 (lines 28 and 29), 7 (lines 15-17), and 15 (lines 5 and 6) do not provide written support for a genus of “CD28 cytoplasmic domains” that are encoded by fragments of CD28 encoded by portions of the polynucleotide sequence of the cDNA encoding CD28, which comprise nucleotides 336-663.

For further clarity, as was previously noted, the originally filed disclosures at pages 6 and 7 contain apparent errors, since each refers to residues 336-663 of the cDNA encoding CD28 as “amino acids”, rather than nucleotides. At page 7, Applicant has amended the disclosure to read, “[a] preferred CD28 moiety is one which spans amino acids encoded by bases 336 to 663 of CD28 cDNA”. It is believed the amendment at page 7 is supported by the original disclosure at page 15 (lines 5 and 6), which reads, “[a] segment of the human CD28 cDNA that encodes part of the extracellular, the transmembrane, and the cytoplasmic domains (amino acids 336 to 663) was amplified [...].” However, in contrast to the original disclosure at page 15, as well as the amended disclosure at page 7, the amended disclosure at page 6 reads, “the CD28 cytoplasmic domain (particularly a fragment encoded by bases **including** bases 336 to 663 of CD28 cDNA” (emphasis added).

Therefore, as also explained in the preceding Office communication, the originally filed disclosure does not provide written support for a genus of “CD28 cytoplasmic domains” that are encoded by fragments of CD28 encoded by portions of the polynucleotide sequence of the cDNA encoding CD28, which comprise nucleotides 336-663. The originally filed disclosure merely provide written support for the CD28

¹ See, e.g., MERRIAM-WEBSTER ONLINE (www.Merriam-Webster.com), which provides the following definition of the noun “span”: “an extent, stretch, reach, or spread between two limits” (copyright 2005 by Merriam-Webster, Incorporated).

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cytoplasmic domain, which is the fragment of CD28 encoded by nucleotides 336 to 663 of the full-length cDNA molecule encoding intact CD28.

Applicant is again required to cancel the new matter in the reply to this Office Action.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed December 15, 2005, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 21, 2005.

For clarity, Application No. 10/448,465 has been abandoned; therefore, the provisional obvious-type double patenting rejection set forth in section 20 of the preceding Office action is moot.

Furthermore, at page 12 of the amendment filed September 15, 2005, Applicant has stated that the instant application and copending Application No. 10/448,256 are not commonly assigned since this application has two assignments, whereas the copending application has only one of these two assignments.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

8. The rejection of claims 1, 12, 13, and 16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning in the sixth paragraph at page 8 of the amendment filed December 15, 2005, Applicant has traversed this ground of rejection.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

² See, e.g., MERRIAM-WEBSTER ONLINE (www.Merriam-Webster.com), which provides the following definition of the transitive verb "span": "to extend across" (copyright 2005 by Merriam-Webster, Incorporated). "Spanning" is the inflected form of the transitive verb.

Applicant has argued that the written description requirement is met because the specification includes the description of "multiple examples" of fusion proteins comprising "a cytoplasmic domain", which according to claim 1 "functions as a transducer of a mammalian immune response in the presence of a costimulatory factor". In reply to this argument, as explained in the preceding Office action mailed September 21, 2005, the claims are directed to a genus of fusion proteins comprising a member of a genus of "cytoplasmic domains", which is only described as a molecule that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor, and which is not described as necessarily having any particularly identifying structural characteristics. Again, the specification includes a description of a few members of the genus of cytoplasmic domains to which the claims are directed, including, in particular, a cytoplasmic domain of the zeta chain of CD3, a cytoplasmic domain of CD28, and a cytoplasmic domain of 4-1BB. The specification discloses that additional, non-limiting examples of suitable cytoplasmic domains include CD40, ICOS and Trance (page 6). Although each of these proteins are known to function as transducers of a mammalian immune response in the presence of a costimulatory factor, *they share no structurally identifying feature*, which serves to delineate them and other members of the genus of cytoplasmic domains to which the claims are directed from other proteins. Moreover, although each acts as a transducer of a mammalian immune response in the presence of a costimulatory factor, each has a markedly different physiologic function. Therefore, given the structural disparity among the different members of the genus, which have been described, despite the fact that each acts as a transducer of a mammalian immune response in the presence of a costimulatory factor, these few members do not appear to adequately represent the genus as a whole, because the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of its members.

Again, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting'

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such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

Therefore, as explained in the preceding Office action, the mere description of a few members of the genus of "cytoplasmic domains", which are structurally and functionally different proteins, is not sufficient to meet the requirements of 35 USC § 112, first paragraph, since the genus embraces widely variant members and an adequate description of such cannot be achieved by describing members, which are not representative of the genus. As disclosed and claimed, the genus does not comprise members having a common, particularly identifying structural feature that correlates with a common functional feature shared by at least a substantial number of its members. As such, absent any of the factual evidence of an actual reduction to practice discussed above, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the claimed genus said at least substantial number. Accordingly, the specification would not reasonably convey to the

skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Applicant has notably cited the recent decision by the Federal Circuit in deciding interference proceedings, namely *Capon v. Eshhar*, 76 USPQ2d 1078 (CA FC 2005) as support for their position that the description of the few exemplary cytoplasmic domains should be regarded as sufficient to satisfy the written description requirement.

First of all, it is aptly noted that the Federal Circuit has stated that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Secondly, in the instance of *Capon v. Eshhar*, the Court concluded, "the Board erred in ruling that §112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, **when that sequence is already known in the field**" (emphasis added). The very notable difference between the issue addressed by the Court in deciding this case and this issue at hand in this application is that, here, the claims are directed to fusion protein comprising "a cytoplasmic domain", wherein "the cytoplasmic domain is the cytoplasmic domain of a molecule which functions as a transducer of a mammalian immune response in the presence of a costimulatory factor". Moreover, here, the claims are not directed to simply a *genus* of "cytoplasmic domains", which is admittedly already known in the field, but rather to any member of a *genus* of cytoplasmic domains of any of a variety of structurally and functionally disparate "molecules", which have only been described as necessarily functioning as a transducer of a mammalian immune response in the presence of a costimulatory factor". These disparate molecules, and their cytoplasmic domains having this functional property, are not limited to those that are *already known*, but instead are reasonably expected to include novel or otherwise poorly characterized molecules having cytoplasmic domains having the ability to transduce a signal in the presence of a costimulatory factor, which leads to a modulation of the mammalian immune response.

In deciding *Capon v. Eshhar*, the Federal Circuit reviewed some relevant prior decisions, which the Court suggests help to define the statutory requirement as it applies to the relevant field of biotechnology:

In *Lilly*, 119 F.3d at 1567, the cDNA for human insulin had never been characterized. Similarly in *Fiers*, 984 F.2d at 1171, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a “wish” or research “plan.” In *Amgen*, 927 F.2d at 1206, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere “wish to know the identity” of the novel material. In *Enzo Biochem*, 296 F.3d at 1326, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 [65 USPQ2d 1385] (Fed. Cir. 2003) the court explained further that the written description requirement may be satisfied “if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.” These evolving principles were applied in *Noelle v. Lederman*, 355 F.3d 1343, 1349 [69 USPQ2d 1508] (Fed. Cir. 2004), where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925-26 [69 USPQ2d 1886] (Fed. Cir. 2004), where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme. *Id.* at 1084.

While in this instance, the Court opined that none of these prior decisions by the Court “require a re-description of what was already known” (*Id.*), it is submitted that these prior decisions establish the written description provision as requiring such a full and adequate description of the subject matter claimed so as to reasonably convey to the skilled artisan that Applicant had possession of that subject matter at the time the application was filed. Moreover, it is submitted these prior decisions establish that a description of that subject matter by its biological function alone would not constitute such a full and adequate description since such a description would represent a mere “wish to know the identity” of the novel material.

“[G]eneralized language may not suffice if it does not convey the detailed identity of an invention.” *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the *genus* of “cytoplasmic domains”, each of which is “the cytoplasmic domain of a molecule which functions as a transducer of a mammalian immune response in the

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presence of a costimulatory molecule". A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

In deciding *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997), the Federal Circuit held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of "cytoplasmic domains" by only their common ability transduce a signal in the presence of a costimulatory molecule that modulates a mammalian immune response does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding molecules comprising "cytoplasmic domains", which transduce a signal to achieve an inhibitory or stimulatory effect upon a mammalian immune response; without such molecules, it is impossible to practice the claimed invention. Although the specification describes "cytoplasmic domains" of a few exemplary molecules (e.g., CD28), which are used to practice the claimed invention, these molecules are not representative of the genus as a whole; and furthermore, the Federal Circuit has decided that a patentee of a

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biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Noelle v. Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Again referring to the *Capon v. Eshhar* decision cited by Applicant, the Court stated: “It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *In re Angstadt*, 537 F.2d 498, 504 [190 USPQ 214] (CCPA 1976)” [underlining added for emphasis]. *Id.* at 1085. While at page 7 the specification describes exemplary “cytoplasmic domains” as comprising the cytoplasmic domains of two well-known molecules (i.e., the zeta (ζ) chain of the T cell receptor (TCR) and the costimulatory factor CD28), it is duly noted that both are described as capable of stimulating, maintaining or enhancing an immune response; in contrast, the claims are not directed to fusion proteins comprising the cytoplasmic domains of molecules that function to stimulate, maintain, or enhance an immune response, but rather encompass fusion proteins comprising any cytoplasmic domain of a molecule, which is capable of functioning a transducer of *any* signal in the presence of a costimulatory factor that affects the immune response in a mammal. The signal transduced by the “cytoplasmic domain” of the claimed fusion protein need not be effective to stimulate, maintain or enhance an immune response; rather it may be inhibitory. As such, giving the claims the broadest, reasonably interpretation, the claims are deemed to encompass fusion proteins comprising the cytoplasmic domains of molecules that function to *suppress* the mammalian immune response; yet, the specification does not describe such fusion proteins or the cytoplasmic domains of molecules that are capable of achieving this effect. Though the claims are directed to fusion proteins comprising “cytoplasmic domains” of molecules, which are not yet known and/or characterized, it is only possible to evaluate the breadth of the claims in light of *known* molecules comprising “cytoplasmic domains” having the capability of transducing a signal in the presence of a costimulatory factor that affects a mammalian

immune response. Thus, for example, the claims are reasonably deemed to encompass a fusion protein comprising the cytoplasmic domain of CTLA-4, which is a molecule having a cytoplasmic domain that functions as a major negative regulator of T cell responses³. However, even a most liberal reading of the specification would not reasonably convey to the skilled artisan that Applicant has contemplated such a fusion protein, as it would not sufficiently demonstrate, or even describe the inhibitory effect of fusion proteins having the ability to transduce a signal that suppresses mammalian immune response, so as to show possession of the claimed genus comprised of such permutations.

Although the skilled artisan could potentially identify molecules comprising cytoplasmic domains, which might be used in practicing the claimed invention to achieve the claimed modulatory effect upon a mammalian immune response, it is duly noted that the written description provision of the statute is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the “written description” inquiry, whatever is now claimed.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Accordingly, although Applicant’s argument has been carefully considered in light of the cited decision of the Federal Circuit, it has not been found persuasive.

³ See, e.g., Teft et al. (*Annu. Rev. Immunol.* 2006 Apr 23; **24**: 65-97) for a review of recent advances in understanding the function of CTLA-4.

Claim Rejections - 35 USC § 103

9. The rejection of claims 1-3, 12, 13, 25; 26, 29, and 30 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2 in view of U.S. Patent No. 5,538,866 A, is maintained.

Beginning in the fifth paragraph at page 9 of the amendment filed December 15, 2005, Applicant has traversed this and the other grounds of rejection under 35 U.S.C. § 103(a).

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

In the second paragraph at page 10 of the amendment Applicant has commented that a copy of a publication by Guest et al. has been submitted; however, a copy of the publication was apparently not provided, nor has the reference been cited as part of an Information Disclosure Statement.

In the third paragraph at page 10 of the amendment Applicant has remarked, obviousness is a legal concept and has contended it is important to remember that the prior art must provide not merely a teaching of the elements of the claimed invention but also a motivation to combine the teachings of the prior art to practice the claimed invention with a reasonable expectation of success. These remarks are acknowledged; however, it is not apparent how these remarks are intended to rebut the *prima facie* case of the obviousness of the claimed invention over the prior art. If by these remarks Applicant intended to argue the artisan of ordinary skill in the art would not have had a reasonable expectation of success, it is duly noted Applicant has not provided any logical or scientific basis supporting such an assertion; nonetheless, as the claims are directed to a fusion protein, because making fusion proteins using recombinant DNA technology was conventional and routine in the art at the time the invention was made, there appears no reason to suspect the artisan would not have had a reasonable expectation of successfully making such a fusion protein.

In the fourth paragraph at page 10 of the amendment Applicant has argued that there is no specific motivation in the prior art to select PSMA, as opposed to any other antigen of interest. In response to this argument, the examiner recognizes that

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obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as explained in the preceding Office action mailed September 21, 2005, Israeli et al. suggests making and using chimeric T cell receptors that incorporate the anti-tumour specificity of a monoclonal antibody that binds PMSA, since hybrid T cells transfected with expression vectors encoding such chimeric T cell receptors could be infused into a patient as a means to direct the cytolytic activity of the T cells to prostate tumors in the patient. Accordingly, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have made peripheral blood lymphocytes transduced with an expression vector encoding a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds PMSA and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are adjoined by a connector comprising a CD8 hinge, because Israeli et al. suggests making such hybrid T cells expressing such fusion proteins (i.e., chimeric T cell receptors) and Bebbington et al. teaches making peripheral blood lymphocytes transduced with an expression vector encoding such a fusion protein, which comprises a scFv that binds any tumor-associated antigen and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are adjoined by a connector comprising a CD8 hinge. As further explained previously, one ordinarily skilled in the art at the time of the invention would have been motivated to do so because the prior art teaches or suggests that transduced peripheral blood lymphocytes expressing such fusion proteins may be used therapeutically to treat prostate cancer.

In the fifth paragraph at page 10 of the amendment Applicant has made remarks, which are interpreted to suggest the conclusion of obviousness is based upon improper hindsight reasoning since the "prior art" teaches the linker is optional and/or not limited to the linker taught by the particular references cited as the basis of this rejection. In

response to Applicant's argument, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, the issue at hand is not whether other "prior art" references may have suggested a fusion protein lacking a linker, but rather whether the prior art cited as the basis of this rejection teaches or suggests a fusion protein comprised of such a linker.

In the sixth paragraph at page 10 of the amendment Applicant has contended that the Examiner has failed to properly take into consideration the characteristics of the claimed fusion proteins in assessing obviousness. In reply, the Examiner disagrees with this contention, which appears to have no factual basis.

10. The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2 in view of U.S. Patent No. 5,538,866 A, as applied to claims 1-3, 12, 13, 25, 26, 29 and 30 above, and further in view of Lams et al. (*Hum. Gene Ther.* 1996 Aug 1; 7 (12): 1415-1422), is maintained.

Beginning in the fifth paragraph at page 9 of the amendment filed December 15, 2005, Applicant has traversed this and the other grounds of rejection under 35 U.S.C. § 103(a).

As explained above, Applicant's arguments have been carefully considered but not found persuasive.

11. The rejection of claims 5, 28, and 32 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2 in view of U.S. Patent No. 5,538,866 A, as applied to claims 1-3, 12, 13, 25, 26, 29 and 30 above, and further in view of Shuford et al. (*J. Exp. Med.* 1997 Jul 7; **186** (1): 47-55), is maintained.

Beginning in the fifth paragraph at page 9 of the amendment filed December 15, 2005, Applicant has traversed this and the other grounds of rejection under 35 U.S.C. § 103(a).

As explained above, Applicant's arguments have been carefully considered but not found persuasive.

Double Patenting

12. The provisional rejection of claims 1-3, 12, 13, 25, 26, 29, and 30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-13, 15-20, 22-30, 32-38, 40-45, and 47-50 of copending Application No. 10/448,256 in view of U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2, is maintained.

Beginning in paragraph 4 at page 11 of the amendment filed September 15, 2005, Applicant has traversed this ground of provisional rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has remarked that the instant application represents "prior art" over copending U.S. Patent Application No. 10/448,256. This point is irrelevant to the issue of double patenting.

Applicant has further remarked that it is presumed claims will not issue in copending application, which are obvious over the disclosure of the present application. In reply, it is not relevant to ponder whether claims will issue in the copending application; furthermore, the issue here is whether or not the subject matter of claims 1-3, 12, 13, 25, 26, 29, and 30 in this application would be obvious over the subject matter of copending claims 1-5, 7-13, 15-20, 22-30, 32-38, 40-45, and 47-50 in view of U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2.

Applicant's remarks in the sixth paragraph at page 11 of the amendment are acknowledged but not well understood because of numerous apparent typographical errors in sentence construction. Nevertheless, it seems probable that Applicant has intended to argue the subject matter of the claims of the copending application are

patentably distinct from the subject matter of the instant claims because the copending claims are directed to fusion proteins comprising *both* the cytoplasmic domain of the zeta chain of TCR and the cytoplasmic domain of CD28. In response to this argument, the instant claims are directed to fusion proteins comprising a cytoplasmic domain.

Then, continuing in the sixth paragraph at page 11 of the amendment, Applicant has asserted the instant claims dominate the copending claims. Contrary to Applicant's assertion, given the minor differences between the subject matter claimed in this application and the copending application, as explained previously, the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application in view of either of the secondary references.

Conclusion

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

[Signature]
Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
May 16, 2006